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REDUCING THE BURDEN OF ANEMIA IN INFANTS AND YOUNG CHILDREN IN MALARIA-ENDEMIC COUNTRIES OF AFRICA: FROM EVIDENCE TO ACTION

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Abstract. Anemia is one of the commonest and most intractable public health problems in Africa. This paper illustrates how, in areas of stable malaria transmission, anemia is apparent from the first few months of life, with the highest prevalence towards the end of the first year. The antenatal and postnatal factors predisposing to anemia in infants and young children are discussed, together with the interventions that are available for prevention. The paper stresses the need to target interventions at pregnant women and infants, the groups at highest risk of anemia, and to develop an integrated, non disease-specific approach to this complex problem.

INTRODUCTION

Anemia (hemoglobin level < 11 g/dL) remains one of the most intractable public health problems in malaria-endemic countries of Africa. It affects more than half of all pregnant women and children less than five years old,[1,2] and has serious consequences since severe anemia (hemoglobin level < 5 g/dL) is associated with an increased risk of death,[3] while iron deficiency and anemia may impair cognitive and motor development,[4–6] growth,[7] immune function,[8] and physical work capacity.[9] The insidious nature of its presentation means, however, that mild-to-moderate degrees of anemia frequently remain undetected and untreated by health care workers and in the community,[10,11] while blood transfusion for severe anemia may be prescribed on the basis of inaccurate hemoglobin measurement,[12] thus exposing the patient unnecessarily to the risk of infection with human immunodeficiency virus (HIV) and other blood-borne pathogens.[13] Prevention is clearly of critical importance, yet current coverage with antimalarial interventions and micronutrient supplementation is poor in many African countries.[14] In these settings, the targeted delivery of interventions against anemia to high-risk groups (pregnant women and young children) may be an appropriate use of limited economic and human resources.

AGE PATTERN OF ANEMIA IN AREAS OF STABLE MALARIA TRANSMISSION

Measurement of hemoglobin on capillary blood using the HemoCue hemoglobinometer (HemoCue AB, Angelholm, Sweden) has been recently introduced as part of nationally representative household-level Demographic and Health Surveys (DHS) (ORC Macro. http://www.measuredhs.com). To date, hemoglobin measurement has been or is currently included in surveys from 13 countries in tropical Africa. Data on children less than five years old from surveys conducted in Benin (n = 2,568), Uganda (n = 6,003), Mali (n = 3,192), and Madagascar (n = 2,272), is shown in Figure 1 (courtesy of Dr. E. Korenromp, Roll Back Malaria Department, World Health Organization, Geneva, Switzerland). The proportion of the population exposed to four or more months of malaria transmission per year ranges from 55.5% (Madagascar) to 86.4% or higher (Uganda, Mali, and Benin).[15] Figure 1a shows that hemoglobin levels continue to decline after the physiologic decrease that normally occurs in the first 2–3 months of life, reaching a nadir towards the end of the first year. Data from Benin and Uganda (Figure 1b) demonstrate that more than 80% of infants 10 months of age are anemic, and approximately one-third have hemoglobin levels less than 8 g/dL. Strikingly similar patterns have been reported from community cross-sectional and cohort studies conducted in areas of stable, perennial malaria transmission in Tanzania,[11,16] Kenya,[17–19] (Figure 2), and Malawi.[20]

THE COMPLEX ETIOLOGY OF ANEMIA

Anemia is usually multi-factorial in origin, and although malaria plays a key etiologic role in endemic countries, it is clear that poor nutritional status, micronutrient deficiencies, intestinal helminths, HIV infection, and hemoglobinopathies make important additional contributions. A number of factors account for the progressive fall in hemoglobin that is observed during the first year of life in areas of stable malaria transmission.

Antenatal factors. *Placental malaria.* Sequestration of malaria parasites in the placenta, a consequence of infection with *Plasmodium falciparum* during pregnancy, is associated with an increased risk of intrauterine growth retardation (IUGR), premature delivery, maternal and infant anemia, and infant mortality.[19,21–23]

Poor maternal nutrition and micronutrient deficiencies. Poor nutritional status in pregnancy has adverse consequences that can persist from one generation to the next, since women who are underweight or stunted are at risk of delivering premature or low birth weight infants, who are themselves at risk of poor growth and development and anemia in childhood and adolescence.[24] Iron deficiency is a common cause of anemia in pregnant women in malaria-endemic areas,[25–28] and a recent study from Malawi demonstrated an absence of stainable iron in bone marrow aspirate, the most definitive method for determining iron status, in 44% of pregnant women with a hemoglobin levels less than < 10.5 g/dL.[28] Multiple micronutrient deficiencies contribute to anemia in pregnancy, and deficiencies of vitamin A, folate, and vitamin B-12 were found in approximately 40%, 30%, and 25%, respectively, of pregnant Malawian women with anemia.[28]

Transfer of iron from the mother to the fetus is regulated by the placenta,[29] with approximately two-thirds of fetal accretion occurring during the third trimester.[30] A recent study from Zimbabwe has shown that maternal anemia and low birth weight are significant predictors of low total body iron (TBI) in infants, with the odds of subsequent anemia at 6, 9, and 12 months of age being more than three times higher in

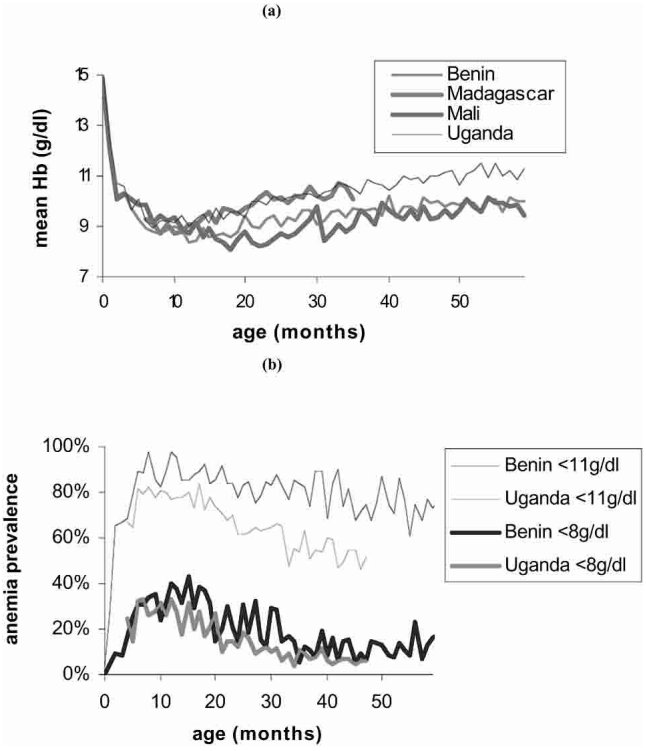

FIGURE 1. Age patterns of anemia in Demographic and Health Surveys (DHS). **a**, mean hemoglobin (Hb) concentration (g/dL). **b**, prevalence of an Hb concentration less than 11 g/dL and 8 g/dL.

infants in the lowest TBI quartile compared with those in the highest quartile.[31] The combination of maternal iron deficiency and placental malaria therefore places infants born to pregnant women in malaria-endemic areas at particularly high risk of developing iron-deficiency anemia during the first year of life.

Human immunodeficiency virus. Infection with HIV in pregnancy is associated with an increased risk of IUGR, premature delivery, and anemia in the pregnant woman and her infant.[19,32–36] There is increasing evidence of adverse interactions between malaria and HIV,[37] which are likely to exacerbate the risk of anemia in the first year of life that arises from either factor independently. Human immunodeficiency virus increases the risk of placental malaria,[35,36] and recent evidence suggests that placental malaria may increase the risk of mother-to-child transmission of HIV,[38] particularly if the density of placental malaria infection is high (Ayisi J. and others, unpublished data).

Intestinal helminths. Infection with hookworm and other intestinal helminths causes gastrointestinal blood loss, malabsorption, and inhibition of appetite, thereby exacerbating micronutrient deficiencies and maternal anemia. Intervention studies suggest that even relatively light hookworm infection in pregnancy may cause decreased fetal growth and weight gain.[39]

Postnatal factors *Malaria.* Infants are vulnerable to malaria from the age of approximately three months, when immunity acquired from the mother is wearing off. Hospital series show that in areas of intense transmission, most cases of severe malarial anemia, blood transfusions, and deaths occur in infants[40–42] and children less than five years old.[43–45] Malaria causes anemia through hemolysis and increased splenic clearance of infected and uninfected red blood cells and cytokine-induced dyserythropoeisis.[46–48] A single overwhelming episode of malaria,[49] or repeated episodes due to reinfection or failure to adequately clear parasitemia as a result of antimalarial drug resistance[50] may result in life-threatening anemia, metabolic acidosis,[51] and, if untreated, death. Severe anemia probably accounts for more than half of all childhood deaths from malaria in Africa,[52] with case fatality rates in hospitals between 8% and 18%.[40,41,45,53–55] Case fatality from

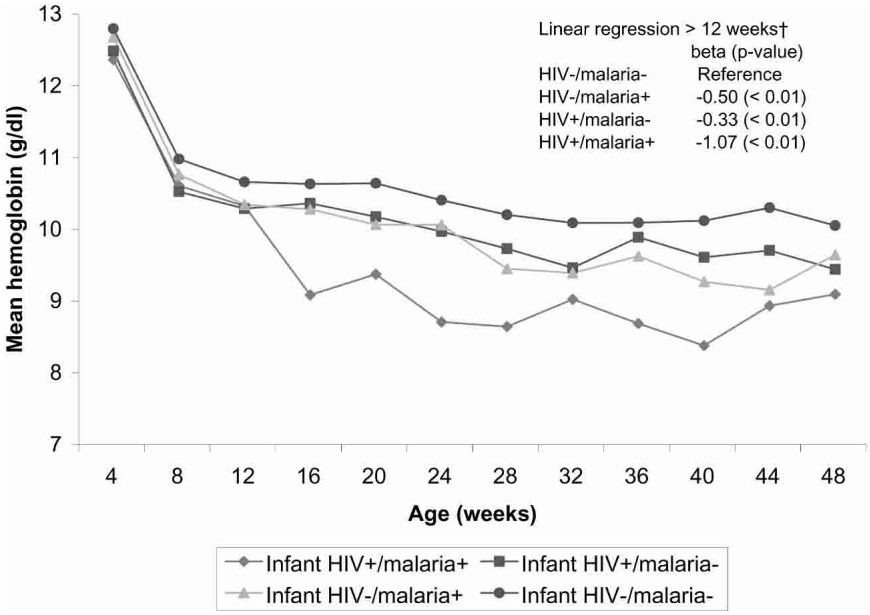

FIGURE 2. Malaria parasitemia and hemoglobin (Hb) levels by HIV status in Kisumu, Kenya, 1996–2000. HIV = human immunodeficiency virus; HIV+ = HIV infected; HIV- = HIV uninfected; malaria+ = parasitemia on blood smear; malaria- = no parasites detected on blood smear. †Linear regression more than 12 weeks adjusted for maternal age, socioeconomic status, placental malaria, sex, small for gestational age, prematurity, history of fever, enlarged spleen, and documented fever. (Reprinted from van Eijk and others[19] with permission of the authors.)

severe anemia in the community is likely to be much higher, since the majority of hospital cases will have received a life-saving blood transfusion.[56]

Human immunodeficiency virus. Infants infected with HIV and malaria are at particular risk of anemia during the first year of life. In a study from an area of high perennial malaria transmission in Western Kenya, a cohort of infants born to HIV-positive and HIV-negative mothers were monitored monthly from birth to one year of age.[19] Mean hemoglobin levels were within the normal range for the first 12 weeks of life, but continued to decrease until 32 weeks of age, when they reached a nadir of 9.9 g/dL. The HIV-infected infants had lower mean hemoglobin levels and significantly more anemia during the first year of life than the uninfected infants. Figure 2 shows the effect of concurrent malaria by age, stratified by HIV status of the infant. Anemia was particularly common in HIV-infected infants with parasitemia at or after 16 weeks, and hemoglobin levels in these infants were significantly lower than those of HIV-uninfected infants or HIV-infected infants without parasitemia ($P < 0.01$).[19] However, early detection and treatment of these infants with antimalarials and iron/folic acid failed to prevent anemia in the majority of cases.[19] Anemia in these infants may be the result of cytokine-mediated inflammation, causing iron sequestration in macrophages, and decreased iron absorption in the small intestine (anemia of inflammation, previously known as anemia of chronic disease).[57–61]

Intestinal helminths. The health consequences of chronic intestinal helminth infections, namely undernutrition, iron deficiency anemia, stunted growth, and impaired cognition,[62,63] are roughly proportional to the intensity of infection.[64] School age children, who harbor the greatest number of worms, and pregnant women are therefore the main focus for helminth control programs.[65,66] In recent surveys, however, the prevalence of intestinal helminth infections in children less than 24 months old has ranged from 2% to 80%.[67] In coastal east Africa, approximately one third of preschool children have hookworm infections, although the intensity of infection is relatively light.[68,69] In populations with a high prevalence of iron deficiency, even light infections may be sufficient to cause anemia.[70]

Poor child nutrition and micronutrient deficiencies. Of the more than 10 million deaths that occur each year in children less than five years old in developing countries, the majority are due to five conditions: malaria, HIV/acquired immunodeficiency virus (AIDS), acute respiratory infections, diarrhea, and measles, and more than half have been attributed directly or indirectly to malnutrition.[71] Poor nutrition and micronutrient deficiencies may exacerbate the severity of any infectious disease,[72,73] and there is increasing evidence that they play an important role in the pathogenesis of malaria and malarial anemia.[74–76]

Many African children live in a state of precarious iron balance. Relatively large amounts of iron are required for erythropoeisis in the first few months of life, and by the age of 4–6 months iron stores are marginal or depleted. Infants with a low TBI as a consequence of low birth weight or maternal iron deficiency[31] are particularly prone to iron deficiency and anemia during this period, and early introduction of cereal-based weaning foods, from which iron absorption can be as low as 5%, may exacerbate the situation further. Iron demand may be further increased by chronic blood loss from the intestine, a result of intestinal helminth infections.

A close association between vitamin A deficiency and anemia has been demonstrated in many nutritional surveys, and a number of intervention studies have documented the impact of improved vitamin A status on hemoglobin levels and anemia.[77] Vitamin A appears to protect against anemia through diverse biologic mechanisms, including the enhancement of the growth and differentiation of erythrocyte progenitor cells, modulation of immunity to infectious diseases, and mobilization of iron stores from tissues.[77] Use of provitamin A carotenoids appears to be increased in children with severe malarial anemia.[78]

Zinc is required for normal immune function, and is essential for the production of interferon-γ, IgG, and tumor necrosis factor-α, all of which are involved in resistance to malaria.[79] Cross-sectional studies in young children in Papua New Guinea and pregnant women in Malawi have demonstrated an association between low zinc status and *P. falciparum* parasitemia.[79,80]

Folate is a central component of erythropoeisis, and hemolysis due to *P. falciparum* stimulates erythroid hyperplasia, making malaria a risk factor for folate deficiency.[81]

Riboflavin deficiency is widespread in populations consuming little milk or meat products, and a high prevalence of biochemical deficiency has been observed in studies from different parts of the developing world.[74,82] Riboflavin deficiency appears to protect against malaria,[83,84] and may impair iron mobilization, globin synthesis, and iron absoption.[82]

Increased production of reactive oxygen species[85] during malaria infection in the presence of inadequate oxidative defense may damage the erythrocyte membrane and contribute towards anemia.[86,87] Alpha-tocopherol is the principal antioxidant in cell membranes, and reduced levels in erythrocyte membranes have been documented in children with malarial anemia.[88] Vitamin C has antioxidant properties, and also facilitates the absorption and mobilization of iron.[82] Evidence from *in vitro* and animal studies suggests that vitamin C deficiency may exacerbate malaria.[74]

INTERVENTIONS TO PREVENT ANEMIA

Antimalarial interventions. Results obtained from malaria intervention studies provide compelling evidence that malaria contributes substantially to anemia in endemic regions. A recent review of 29 community-based studies of insecticide-treated nets (ITNs), antimalarial chemoprophylaxis, and insecticide residual spraying found that among children less than five years old exposed to between one and two years of malaria control, the mean relative risk for a hemoglobin level less than < 11 g/dL was 0.73 (95% confidence interval [CI] = 0.64–0.81) and the mean relative risk for a hemoglobin level less than < 8 g/dL was 0.40 (95% CI = 0.25–0.55) compared with control groups not exposed to malaria interventions (Korenromp E and others, unpublished data).

Insecticide-treated nets. A series of randomized controlled trials of ITNs conducted in areas of stable transmission in Africa has demonstrated that use of ITNs can reduce all-cause child mortality by approximately one-fifth, saving an average of 6 lives for every 1,000 children 1–59 months old protected each year.[89] A recently published trial from a high transmission setting in western Kenya found that the protec-

tive efficacy of ITNs was highest in infants 1–11 months old compared with older children.[90] The ITNs delayed the median time to first parasitemia from 4.5 to 10.7 months, and reduced the incidence of both clinical malaria and anemia by 60%, the reduction being greatest in infants 1–3 months of age.[91] Infants sleeping under ITNs experienced better height and weight gain. The odds of a hemoglobin level less than < 9 g/dL increased with distance from the nearest netted village, indicating that persons not sleeping under ITNs, but living in the immediate vicinity of a netted village, also derived some benefit.[92] When used by women during their first four pregnancies, ITNs reduced maternal parasitemia and placental parasitemia by 35%, and low birth weight by 28%.[93] Mean hemoglobin levels were 0.6 g/dL higher in pregnant women sleeping under ITNs compared with the control group. At an annual cost (1996 rates) of US $25 per life-year gained, ITNs represent a highly cost-effective use of scarce health care resources.[94] Despite these clear health benefits, ITN coverage is still poor in malaria-endemic countries of Africa, and surveys carried out between 1998 and 2001 indicate that 5% of pregnant women and less than 2% of children less than five years old were sleeping under ITNs.[14,95] The challenge is to now increase coverage, particularly among infants and pregnant women in areas of high transmission. This will require large-scale expansion of supply and distribution, strategies to reduce the price of ITNs, and the development of long-lasting insecticidal nets (factory pretreated nets that require no further treatment of their expected lifespan of 4–5 years).[96]

Chemoprophylaxis and intermittent preventive treatment. *Pregnant women.* The use of antimalarial drugs for chemoprophylaxis to prevent *P. falciparum* infection in pregnant women was first reported from Nigeria in 1964.[97] Subsequent studies in several African countries have confirmed the beneficial impact of chemoprophylaxis on birth weight[98] and maternal hemoglobin levels.[99] On the basis of these trials, the World Health Organization (WHO) previously recommended that all pregnant women resident in areas of moderate or high malaria transmission be given chemoprophylaxis with chloroquine throughout the second and third trimesters of pregnancy. However, the effectiveness of this intervention has been seriously compromised by problems of compliance with a weekly drug regimen, the emergence of chloroquine-resistant *P. falciparum* malaria, and by concerns about increasing drug pressure from sub-therapeutic dosing. The WHO now recommends that intermittent preventive treatment (IPT), which provides similar benefits to chemoprophylaxis but reduces some of its risks, be given to pregnant women in areas of stable malaria.[100]

Use of IPT involves the administration of a full therapeutic dose of an antimalarial drug to pregnant women at specified intervals in the second and third trimesters, regardless of whether they are infected. Use of a single-dose drug such as sulfadoxine-pyrimethamine allows all doses to be given under direct observation in the antenatal clinic, and avoids the compliance problems associated with chemoprophylaxis. Presently, sulfadoxine-pyrimethamine is the only antimalarial for which data on efficacy and safety is available from controlled clinical trials. Studies in areas of Kenya and Malawi with low resistance to sulfadoxine-pyrimethamine have shown that IPT with sulfadoxine-pyrimethamine reduces maternal anemia (hemoglobin level less than < 8 g/dL),[101] placental malaria,[102] and low birth weight[103] by approximately 40%. Sulfonamides and pyrimethamine are considered safe in the second and third trimesters of pregnancy.[104] In areas of Africa where resistance to sulfadoxine-pyrimethamine is intensifying, alternative drugs for IPT in pregnancy require urgent evaluation. Since it is not known whether IPT achieves its effect primarily through clearance of parasites or through the long-acting prophylactic effect of sulfadoxine-pyrimethamine, there is also a need to evaluate antimalarials with shorter half-lives for use as IPT.[105] At a cost of US $11 (1997 rates) for the prevention of each disability-adjusted life year due to low birth weight,[106] IPT with intermittent sulfadoxine-pyrimethamine is one of the most cost-effective strategies for preventing morbidity and mortality associated with malaria.[107] Although the proportion of women attending antenatal clinics who receive IPT varies from < 5% to > 70% in different countries,[14,95] experience from Malawi suggests that improved education on the benefits of IPT and modifications to the scheduling of antenatal clinic visits can markedly improve coverage.[14]

Infants. The efficacy of chemoprophylaxis in children was first reported in 1956 from a trial in The Gambia.[108] Children who were given chloroquine weekly from birth until the age of two years had fewer episodes of malaria, better growth, and higher hemoglobin levels than the control group. In Liberia, monthly chloroquine given to children 2–9 years old reduced the number of episodes of clinical malaria by 50% and was associated with a significant improvement in hemoglobin levels.[109] A study conducted in an area of intense transmission in southern Tanzania demonstrated a 60% reduction in episodes of clinical malaria and anemia in infants given weekly pyrimethamine plus dapsone between the ages of 2 and 10 months, although rates increased in the 11 month period after stopping chemoprophylaxis,[110] raising the question as to whether IPT could have a beneficial effect on malaria and anemia without the rebound associated with weekly chemoprophylaxis.

A randomized controlled study from the same study site in Tanzania showed that a single dose of sulfadoxine-pyrimethamine given to asymptomatic infants attending for routine vaccination at two, three, and nine months of age reduced episodes of clinical malaria by 59% and episodes of anemia by 50% during the first year of life.[111] Similar results were obtained from a study conducted in northern Tanzania using amodiaquine.[112] Use of IPT in infants (IPTi) is a particularly attractive strategy, since sustainable delivery may be achieved through the Expanded Program on Immunization (EPI), but a number of important questions need to be addressed before it can be considered for inclusion in national malaria control policies. Will it work in other epidemiologic settings? Is it safe? Might it have an adverse impact on serologic responses to EPI vaccines or on the development of malarial immunity? Is it operationally feasible and cost-effective? The IPTi Consortium, comprising a number of research groups in Africa, Europe, and the United States, together with WHO and the United Nations Children's Fund, has been established to ensure that these issues are addressed in a systematic and timely manner, and has received support from the Bill and Melinda Gates Foundation.

Prompt, effective treatment of malaria infections. Prompt treatment of malaria infections with effective, fast-acting antimalarial drugs rapidly reduces symptomatic high density parasitemia and clears parasites from the blood, allowing erythrocyte numbers to be restored[49,50,113] and reducing the

risk of anemia. The recent spread of antimalarial drug resistance, which has reduced drug efficacy and increased recrudescent parasitemia and anemia,[114,115] is likely to have contributed to the increase in malaria-specific mortality that has been observed in African children over the last decade.[116,117] The rapid action and anti-gametocyte properties of the artemisinin derivatives make them a particularly promising treatment option, and WHO strongly recommends that malaria-endemic countries changing antimalarial drug policy because of increasing drug resistance consider adopting artemisinin-based combination therapy as a first-line treatment for *P. falciparum* malaria.[118] The high cure rates achieved with these combinations[119] and the prospect of sustained efficacy is likely to markedly reduce anemia due to parasite recrudescence.

Intestinal helminths. There is increasing evidence that very young children may benefit from de-worming.[69,120] In a recent study from Zanzibar, the prevalence of moderate anemia (hemoglobin level < 9 g/dL) and wasting (weight-for-height < -1 Z-score and mid upper arm circumference < 5th centile) was significantly reduced in children less than 24 months old with light worm infections who had been treated with mebendazole every three months for a year.[69] In the same study, low dose daily iron supplementation improved iron status and appetite, but had no impact on anemia. First-time helminth infections at this age may induce proinflammatory mediators that are detrimental to protein metabolism, appetite, and erythropoiesis.[121,122] Mebendazole and albendazole can be safely used in young children,[67] and the WHO now recommends that in areas with a high prevalence of intestinal helminths, de-worming three times per year should start from the age of 12 months.[123]

Human immunodeficiency virus. Endogenous release of proinflammatory cytokines (interferon-γ, tumor necrosis factor-α, interleukin-6) and altered iron metabolism are thought to contribute to anemia in HIV-infected individuals.[57,59,124] Increasing use of antiretroviral treatment to prevent mother to child transmission of HIV[125,126] may reduce the prevalence of anemia in infants in populations in which HIV seroprevalence is high.

Micronutrient deficiencies. *Iron.* The role of iron in the prevention and treatment of anemia in malaria-endemic regions remains a highly contentious issue. Iron is a key functional component of a wide range of biologic systems, and is therefore an essential element for nearly all living organisms.[127] Excessive iron can, however, cause tissue damage, since it has the ability to catalyze the generation of reactive free radicals. Regulation of iron metabolism within the body is therefore kept under tight homeostatic control.[128]

Anemia can result from the alterations in iron metabolism that occur as a response to many infectious diseases. Infections and inflammatory diseases decrease iron absorption in the small intestine, and induce iron sequestration in macrophages, the hallmark of anemia of inflammation. It is assumed that the iron sequestration response may increase resistance to infections by restricting the availability of iron to microbes.[60] In the past three years, enormous progress in the understanding of this process has been made by the discovery of hepcidin, an iron-regulatory peptide made by hepatocytes.[61] Exposure of hepatic Kupffer cells to microbes causes the release of interleukin-6, and possibly other cytokines, which induces the synthesis and secretion of hepcidin.[129] Plasma hepcidin inhibits iron uptake in the duodenum and iron release from macrophages in the spleen and elsewhere. The continuing debate on the role of iron in environments where there is a high degree of exposure to infectious diseases (malaria, HIV, bacterial pathogens) is therefore fuelled by the following paradox: although iron deficiency adversely affects growth, immune function, and cognitive development and can cause anemia, the administration of iron for the treatment of anemia may exacerbate infectious disease.

A number of recent reviews have assessed the impact of iron, administered during randomized controlled trials to prevent or to treat anemia, on malaria and other infectious diseases.[8,130,131] Administration of iron has a beneficial, although variable, impact on hemoglobin levels, but appears to increase the risk of diarrhea (incidence rate ratio = 1.11 [95% CI = 1.01–1.23, $P = 0.04$]).[131] The risk of malaria parasitemia is not increased by iron supplementation, once baseline parasitemia is taken into account.[130,131] However, the clinical significance of these findings is unclear since the component studies were not designed and not powered to assess the impact of iron on morbidity and mortality from malaria.

What practical conclusions can be derived from these findings? Iron deficiency is highly prevalent in many malaria-endemic regions of Africa, and it is clear that many infants, particularly those born prematurely or with low birth weight, have low total body iron, and are at particular risk of iron deficiency during the first six months of life. Malaria and other infectious diseases have an adverse impact on hemoglobin levels from the age of approximately three months, and the prevalence of all grades of anemia is highest in the second half of infancy. A short period of iron supplementation in the first few months of life might replenish iron stores at a time when there is less pressure from infectious diseases such as malaria. Among a group of 411 Tanzanian infants who received iron supplementation or placebo between the ages of two and six months as part of a trial to prevent malaria and anemia, and who were followed-up over a period of four years, there was no increase in clinical malaria or outpatient attendance among the iron-supplemented infants (Menendez C, unpublished data). There was a 29% reduction in anemia (packed cell volume < 25%) at the age of one year in infants who had received iron in early infancy,[110] and the cumulative risk of anemia in this group over the four-year period of follow-up was reduced by 18%. An advantage of this strategy is that iron supplementation may be delivered though the EPI,[111] which enhances sustainability and cost-effectiveness.[132] Concurrent delivery of ITNs and, in the future, IPTi, would reduce exposure to malaria during and after the period of iron administration.

Other micronutrients. Although there is a considerable body of experimental evidence to suggest that micronutrient deficiencies may play an important role in the pathogenesis of malaria and malarial anemia, the complex pathways through which micronutrients may influence malaria parasites and host morbidity are poorly understood.[74] A limited number of trials have assessed the impact of micronutrient supplementation on malaria and malarial anemia.

Vitamin A supplementation reduced episodes of clinical malaria in children in Papua New Guinea,[133] although there was no impact on anemia at cross-sectional survey. No impact on clinical malaria was observed in trials of vitamin A supplementation in Ghana and Tanzania.[134,135] However, vitamin A

supplementation has been shown to reduce child mortality,[136] and routine supplementation of pregnant and postpartum women and young children is now recommended.[137]

Although zinc supplementation reduces episodes of diarrhea and pneumonia in young children, the three studies that have assessed the impact of zinc supplementation on the prevention of malaria have yielded conflicting results. A study from Papua New Guinea[138] reported a 38% reduction in episodes of clinical malaria in preschool children given a daily zinc supplement for 11 months, but episodes of clinical malaria were not significantly reduced by zinc supplementation in preschool children in The Gambia [139]and Burkina Faso.[140]

The development of innovative ways of increasing the sustainable delivery of individual and multiple micronutrients is of considerable current interest. Food fortification,[141] the use of complementary food supplements (micronutrient sprinkles, fortified spreads),[142] and the breeding of crops with an increased content of specific micronutrients[143] are strategies that appear particularly promising. Increased communication and collaboration between the nutrition, agriculture, and development sectors is an essential prerequisite of improving dietary quality for poor populations.[144]

PUTTING IT ALL TOGETHER: THE NEED FOR ANEMIA PREVENTION PROGRAMS

Despite the magnitude of the anemia problem, and the constantly expanding body of research findings relating to pathogenesis, risk factors, and efficacious interventions, coverage of interventions to prevent anemia in malaria-endemic countries remains poor.[14] This is due largely to the fact that all of the currently available interventions against anemia fail to fulfill one or more of the following criteria that help to determine whether a health care strategy is successfully introduced at country level. First, there must be convincing data relating to efficacy and safety. A balance must be struck between the need for further research, and the timely development of clear policy recommendations. The translation of research into policy should be an iterative process, enabling policy guidelines to be modified in relation to relevant new research findings.[145] Second, an intervention must be cost-effective and affordable. "Affordability" is a function of political and financial commitment on the part of national governments and donor agencies. Third, it must be readily available at health facilities, which requires detailed planning and functional health systems, and, lastly, it should be delivered through systems that are sustainable in the long term. The complex, multifactorial nature of anemia in malaria-endemic regions of Africa means that it is best tackled by means of an integrated, non–disease-specific approach. This approach is more likely to be successful if interventions are targeted at the groups at highest risk of anemia, namely pregnant women and their infants, and if sustainable systems, namely antenatal clinics and the EPI, are used for their delivery. National survey data from 28 African countries indicate that in general, antenatal clinic attendance exceeds 70%.[14] The EPI coverage, although variable, reaches 60% or more in the majority of African countries. Both systems could be used for the delivery of ITNs, IPT, pre-packaged antimalarial drugs for emergency use at home, de-worming, micronutrient supplementation, dietary advice, and, potentially, antiretroviral therapy. Although it is clearly important to avoid overloading existing systems, this approach might have the advantage of increasing attendance at these routine points of contact with health services. The substantial increase in financial and human resources that will be necessary to achieve the current goal of rapidly increasing access to antiretroviral drugs in Africa[146] should be viewed as an excellent opportunity for improving the prevention and treatment of anemia, and for strengthening maternal and child health services. Establishing strong linkages between relevant programs (Maternal and Child Health, EPI, Roll Back Malaria, HIV/AIDS, and others) at national, regional, and international level will be an important part of this process.

Although prevention is of utmost importance, there are additional challenges that must be addressed. More emphasis needs to be placed on increasing awareness of anemia in the community and by health care workers, since mild and moderate degrees of anemia may, if unrecognized and untreated,[10,11] progress to severe, life-threatening anemia. Efforts should be made to ensure that laboratories at district hospital level use an accurate, user-friendly, and, ideally, inexpensive method for measuring hemoglobin, since blood transfusions that are prescribed on the basis of faulty hemoglobin measurement[12] expose the patient unnecessarily to the risk of HIV and other blood-borne diseases.[13] Hospital clinicians need to be trained to recognize the clinical features that are associated with increased mortality from severe anemia,[147] and there is a need to develop transfusion guidelines that are based on clinical criteria, and not solely on the level of hemoglobin.[148] Although blood transfusion for severe anemia can be life-saving,[56] the optimal speed and volume of transfusion remain to be determined.[51] The spread of HIV infection increases the urgency of exploring alternatives to blood for the treatment of severe anemia, and the recent development of modified hemoglobin blood substitutes[149] is therefore timely.

CONCLUSIONS

It is clear that an integrated, non disease-specific approach is essential if the intolerable burden of anemia that currently exists in malaria-endemic regions of Africa is going to be reduced. It will be important to involve health programs as diverse as malaria, nutrition, reproductive and child health, HIV/AIDS, helminth control, and laboratory and blood transfusion services. There needs to be communication and collaboration with other disciplines, particularly environmental health and agriculture.[144,150] Research institutions, nongovernmental organizations and the media have important roles to play. Political will is essential: ministers of health and finance need to understand that anemia control is cost-effective and yields substantial health benefits.

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